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119 PCT/EP 01/03481 (3/27/01)

PCT/IB00/00849 6/26/00

WO 01/02007 13 in the title

119 WO 0123425

Also 23457 searches, no print out

09/840341 fd 4-23-01

File 5:Biosis Previews(R) 1969-2003/Nov W2

*File 5: BIOSIS Previews has been reloaded with major enhancements.
See HELP NEWS005 for more information.

Set	Items	Description
S1	5690	PLASMINOGEN NOT (PLASMINOGEN()ACTIVATOR?)
S2	5780	PRION
S3	11	S1 AND S2
S4	316	AU='AGUZZI A' OR AU='AGUZZI ADRIANO'
S5	107	S4 AND PRION
S6	6	S4 AND PLASMINOGEN

? t s3/7/1-11

3/7/1
DIALOG(R)File 5:Biosis Previews(R)

0014392035 BIOSIS NO.: 200300350754
The fate of the %%%prion%%% protein in the %%%prion%%%/%%%plasminogen%%% complex.
AUTHOR: Kornblatt Jack A (Reprint); Marchal Stephane; Rezaei Human; Kornblatt M Judith; Balny Claude; Lange Reinhard; Debey Marie-Pascale; Hoa Gaston Hui Bon; Marden Michael C; Grosclaude Jeanne
AUTHOR ADDRESS: Concordia University, 1455 de Maisonneuve Blvd., Montreal, PQ, H3G 1M8, Canada**Canada
AUTHOR E-MAIL ADDRESS: krnbltt@vax2.concordia.ca
JOURNAL: Biochemical and Biophysical Research Communications 305 (3): p 518-522 June 6, 2003 2003
MEDIUM: print
ISSN: 0006-291X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The cellular %%%prion%%% protein (PrPc) forms complexes with %%%plasminogen%%%. Here, we show that the PrPc in this complex is cleaved to yield fragments of PrPc. The cleavage is accelerated by plasmin but does not appear to be dependent on it.

3/7/2
DIALOG(R)File 5:Biosis Previews(R)

0014081196 BIOSIS NO.: 200300049915
Overexpressed protein disulfide isomerase in brains of patients with sporadic Creutzfeldt-Jakob disease.
AUTHOR: Yoo Byong Chul; Krapfenbauer Kurt; Cairns Nigel; Belay Girma; Bajo Michal; Lubec Gert (Reprint)
AUTHOR ADDRESS: Department of Pediatrics, University of Vienna, Waehringer Guertel 18, A-1090, Vienna, Austria**Austria
AUTHOR E-MAIL ADDRESS: gert.lubec@akh-wien.ac.at
JOURNAL: Neuroscience Letters 334 (3): p196-200 December 16, 2002 2002
MEDIUM: print
ISSN: 0304-3940 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Earlier studies have failed to detect covalent modifications in beta-sheet-rich scrapie isoform %%%prion%%% protein (PrPSc) and have concluded that the conversion of alpha-helix-rich cellular form %%%prion%%% protein (PrPC) to PrPSc represents purely conformational transition not involving chemical reactions. However, recent studies have shown that the intradisulfide bond of PrPC can play an important role for instability and conformational change to PrPSc. Interestingly, we found overexpressed protein disufide isomerase (PDI) in brains of sporadic Creutzfeldt-Jakob disease (sCJD, human %%%prion%%% disease) patients using two dimensional electrophoresis and Western blot analysis but not in other neurodegenerative disorders as Down Syndrome and Alzheimer's disease. However, proteinase K digestion and %%%plasminogen%%% binding assay of brain homogenates incubated with PDI suggest that PDI has no effect on either proteinase resistance or conformational change of PrP. Overexpression of PDI protein in sCJD brain may simply reflect a cellular defense response against the altered %%%prion%%% protein.

3/7/3
DIALOG(R)File 5:Biosis Previews(R)

0013962178 BIOSIS NO.: 200200555689
Prions: Health scare and biological challenge
AUTHOR: Aguzzi A (Reprint)
AUTHOR ADDRESS: Univ. Spital Zurich, Zurich, Switzerland**Switzerland
JOURNAL: Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy 41 p516 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 41st Annual Meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy Chicago, Illinois, USA September 22-25, 2001; 20010922
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Mice deficient in the normal %%%prion%%% protein are resistant to exposure to %%%prion%%% infectivity, and expression of the normal %%%prion%%% protein by neurons is necessary for the development of histological damage. But how do prions reach the brain after entering the body from peripheral sites? Neuroinvasion, i.e. the process by which prions march through the body of the host towards the brain, is dependent upon expression of the normal %%%prion%%% protein in a non-hematopoietic extracerebral site. We therefore developed the hypothesis that neuroinvasion takes place in two distinct steps: first the lymphoreticular system is diffusely colonized by the agent, while at a later time infectivity progresses from lymphoreticular organs to the central nervous system, possibly via peripheral nerves. There is an absolute requirement for B-lymphocytes in peripheral %%%prion%%% pathogenesis. Surprisingly, the presence of the normal %%%prion%%% protein is not necessary on B-lymphocytes to enable them to support this process. The mechanism of action of B lymphocytes may consist of presentation of lymphotoxin-beta to follicular dendritic cells. This paves the way to post-exposure prophylaxis strategies that exploit the anti-%%%prion%%% effect of soluble lymphotoxin-beta receptors. Why do follicular dendritic cells accumulate prions? We tested the hypothesis that %%%prion%%% uptake may be complement-mediated. Indeed, certain components of the complement system (C1q, CR1/2) proved to play an important role in pathogenesis. Progress in the understanding of pathogenesis and a elucidation of possible therapeutical and prophylactic approaches must go hand-in-hand with diagnostic procedures. With this in mind, we initiated a screen for plasma proteins that bind specifically

disease-associated %%%prion%%% protein. %%%Plasminogen%%% was identified as such a protein. No other reagent has been shown to differentially bind the pathological %%%prion%%% protein while disregarding its normal counterpart. This fact may be exploitable as the basis of a sensitive diagnostic assay for BSE and for human %%%prion%%% diseases.

3/7/4
DIALOG(R)File 5:Biosis Previews(R)

0013843899 BIOSIS NO.: 200200437410
The binding of %%%prion%%% proteins to serum components is affected by detergent extraction conditions
AUTHOR: Shaked Yuval; Engelstein Roni; Gabizon Ruth (Reprint)
AUTHOR ADDRESS: Department of Neurology, Hadassah University Hospital, Jerusalem, 91120, Israel**Israel
JOURNAL: Journal of Neurochemistry 82 (1): p1-5 July, 2002 2002
MEDIUM: print
ISSN: 0022-3042
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: As many GPI anchored proteins, PrPC and its abnormal conformer PrPSc, are inserted into membrane microdomains known as rafts. Upon raft disruption, PrPC becomes soluble, while PrPSc aggregates into insoluble structures. It was recently published that, as opposed to PrPC, PrPSc, as well as its protease resistant core PrP27-30, can bind specifically to %%%plasminogen%%% and other serum components. These findings were suggested to have important physiological implications in transmissible spongiform encephalopathies (TSE) diagnosis and pathogenesis. In this work, we show that the binding of PrPSc or PrP 27-30 to serum proteins occurs only at specific detergent combinations, in which disease associated PrPs are present in aggregated structures. At detergent conditions in which rafts are intact, it is actually PrPC that binds to blood proteins, albeit not directly, but through neighboring rafts components. Our results therefore indicate that the binding of PrPSc to blood components has no physiological relevance.

3/7/5
DIALOG(R)File 5:Biosis Previews(R)

0013786081 BIOSIS NO.: 200200379592
%%%Plasminogen%%% activation is stimulated by %%%prion%%% protein and regulated in a copper-dependent manner
AUTHOR: Ellis Vincent (Reprint); Daniels Maki; Misra Rashmi; Brown David R
AUTHOR ADDRESS: School of Biological Sciences, University of East Anglia, Norwich, UK**UK
JOURNAL: Biochemistry 41 (22): p6891-6896 June 4, 2002 2002
MEDIUM: print
ISSN: 0006-2960
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Prion%%% diseases are associated with the conversion of the normal %%%prion%%% protein, PrPC, to the infectious disease form PrPSc. Discrimination between these isoforms would significantly enhance diagnosis of these diseases, and it has recently been reported that PrPSc is specifically recognized by the serine protease zymogen

%%%plasminogen%%% (Fischer et al. (2000) Nature 408, 479). Here we have tested the hypothesis that PrP is a regulator of the %%%plasminogen%%% activation system. The effect of recombinant PrP, either containing copper (holo-PrP) or devoid of it (apo-PrP), on %%%plasminogen%%% activation by both uPA and tPA was determined. PrP had no effect on %%%plasminogen%%% activation by uPA. By contrast, the activity of tPA was stimulated by up to 280-fold. This was observed only with the apo-PrP isoforms. The copper-binding octapeptide repeat region of PrP was involved in the effects, as a mutant lacking this region failed to stimulate %%%plasminogen%%% activation, although a synthetic peptide corresponding to this region was unable to stimulate tPA activity. Competition experiments demonstrated that, in addition to %%%plasminogen%%% binding, the stimulation required a high-affinity interaction between tPA and PrP (Kd<2.5 nM). Kinetic analysis revealed a template mechanism for the stimulation, suggesting independent binding sites for tPA and %%%plasminogen%%%. Lack of copper-binding may be an early event in the conversion of PrPC to PrPSc, and our data therefore suggest that tPA-catalyzed %%%plasminogen%%% activation may provide the basis for a sensitive detection system for the early stages of %%%prion%%% diseases and also play a role in the pathogenesis of these diseases.

3/7/6
DIALOG(R)File 5:Biosis Previews(R)

0013737405 BIOSIS NO.: 200200330916
Mechanisms regulating pericellular plasmin generation
AUTHOR: Ellis V (Reprint)
AUTHOR ADDRESS: School of Biological Sciences, University of East Anglia, Norwich, NR4 7TJ, UK**UK
JOURNAL: Biochemical Society Transactions 30 (1): pA16 2002 2002
MEDIUM: print
CONFERENCE/MEETING: 675th Meeting of the Biochemical Society joint with the Physiological Society York, England, UK December 18-19, 2001; 20011218
ISSN: 0300-5127
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

3/7/7
DIALOG(R)File 5:Biosis Previews(R)

0013558297 BIOSIS NO.: 200200151808
Selective binding of disease-associated %%%prion%%% protein to %%%plasminogen%%% and other proteins occurs only in the presence of detergents
AUTHOR: Vey Martin (Reprint); Seyfert-Brandt Waltraud (Reprint); Vogel Edwin (Reprint); Baron Henry; Roemisch Juergen (Reprint); Groener Albrecht (Reprint)
AUTHOR ADDRESS: Aventis Behring GmbH, Marburg, Germany**Germany
JOURNAL: Blood 98 (11 Part 2): p112b November 16, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 43rd Annual Meeting of the American Society of Hematology, Part 2 Orlando, Florida, USA December 07-11, 2001; 20011207
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Prion%%% diseases are transmissible, neurodegenerative diseases caused by an infectious protein termed PrPSc. PrPSc is hydrophobic and insoluble in non-denaturing detergents. A recent report on the binding of PrPSc to plasma proteins on magnetic beads in the presence of detergents (Fischer et al., 2000; Nature) has led to the perception that certain plasma proteins, especially %%%plasminogen%%%, might be capable of binding selectively to prions also under physiological conditions. Here we show that prions do not co-fractionate with %%%plasminogen%%% during production of plasma proteins. Spiking studies using %%%prion%%% preparations of increasing purity clearly demonstrate that prions partition with fraction I of Cohn fractionation whereas %%%plasminogen%%% predominantly precipitates in fraction II+III. We further demonstrate that selective binding only occurs in the presence of high concentrations of detergents, which do not exist in manufacturing processes. In the absence of detergent, we found %%%prion%%%-containing brain homogenates to be attached to many other proteins conjugated to magnetic beads. In addition to plasma proteins, certain non-plasma proteins show very similar binding characteristics compared to %%%plasminogen%%%. The data clearly demonstrate that selective binding of proteins to prions is facilitated by high concentrations of detergent.

3/7/8
DIALOG(R)File 5:Biosis Previews(R)

0013558291 BIOSIS NO.: 200200151802
Evaluation of the diagnostic and therapeutic potential of solid phase-bound %%%plasminogen%%%
AUTHOR: Sivakumaran Muttuswamy (Reprint); Saunders Paul (Reprint)
AUTHOR ADDRESS: Department of Haematology, Peterborough District Hospital, Peterborough, Cambridgeshire, UK**UK
JOURNAL: Blood 98 (11 Part 2): p110b-111b November 16, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 43rd Annual Meeting of the American Society of Hematology, Part 2 Orlando, Florida, USA December 07-11, 2001; 20011207
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A recent finding that %%%plasminogen%%% binds the abnormal %%%prion%%% isomer (PrPSc) but not the normal counterpart (PrPc) has led to claims that solid phase-bound %%%plasminogen%%% (SPBP) could be used to develop a blood test for variant Creutzfeldt-Jakob disease (vCJD) and to remove abnormal prions from blood-derived biological products (Fischer et al, Nature 2000, 408, 479-483). However, the diagnostic and therapeutic potential of this approach will depend on the reactivity of SPBP to other cellular and plasma-derived proteins. We carried out an in-vitro experiment to study the binding of SPBP to various blood cells and cell fragments using %%%plasminogen%%% coated polymer beads (Polybeads) and pooled peripheral blood buffy coat preparations (6 donors) containing intact and fragmented leucocytes and platelets. %%%Plasminogen%%% (10mg/ml) was coated on to the Polybeads using the manufacturer's instructions. Cell fragments were prepared by gentle disruption of the cells using liquid nitrogen. Aliquots of intact cells and cell fragments were washed three times in phosphate buffered saline to remove plasma proteins. 25ul of %%%plasminogen%%% coated Polybeads were incubated with 500ul of 1) unwashed intact buffy coat cells, 2) unwashed cell fragments, 3) washed intact BC cells and 4) washed cell fragments overnight at 4C. Uncoated beads were used as negative control.

The experiments were carried out in duplicates. The reaction mixes were examined by light microscopy, histochemistry (haematoxylin/eosin and Trichrome) and transmission electron microscopy (TEM). The results show that SPBP binds intact blood cells and cellular fragments. The binding is pronounced in the presence of plasma proteins. In addition, SPBP exhibits a tendency to cause precipitation of cellular fragments and plasma proteins, and degradation of fibrinogen leading to fibrin deposition. Based on these findings, we conclude that, because of the non-specific interaction between SPBP and cellular and plasma-derived proteins, a %%%plasminogen%%% based vCJD test may not be specific enough for routine clinical use such as blood donor screening. Furthermore, SPBP is unlikely to prove useful to remove abnormal prions from blood products because of the non-specific binding and proteolytic properties of %%%plasminogen%%%.

3/7/9
DIALOG(R)File 5:Biosis Previews(R)

0013558280 BIOSIS NO.: 200200151791
Quantitation of %%%plasminogen%%% in plasma derived fractions and products using a novel ultra-sensitive immunoassay
AUTHOR: Roemisch Juergen (Reprint); Feussner Annette (Reprint); Muth-Naumann Gudrun (Reprint); Metzner Hubert (Reprint); Vey Martin; Lang Wiegand (Reprint)
AUTHOR ADDRESS: Research, Aventis Behring GmbH, Marburg, Germany**Germany
JOURNAL: Blood 98 (11 Part 2): p108b November 16, 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 43rd Annual Meeting of the American Society of Hematology, Part 2 Orlando, Florida, USA December 07-11, 2001; 20011207
SPONSOR: American Society of Hematology
ISSN: 0006-4971
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Plasminogen%%%, the key enzyme of fibrinolysis, and in particular its kringle domains I-III, have been reported recently to interact with the pathogenic %%%prion%%% protein PrPSc, but not with its normal cellular isoform PrPc. This finding might offer a diagnostic tool to discriminate both conformations. However, binding occurred under highly artificial conditions not reflecting the physiological situation in blood or plasma, or under conditions encountered in plasma protein purification. Nevertheless, an ultra-sensitive ELISA was developed suitable to quantify trace amounts of %%%plasminogen%%% in plasma and derived sub-fractions. Intra- and inter-assay coefficients of variation were below 8%. The specificity was confirmed by spiking experiments using %%%plasminogen%%%-deficient plasmas. The sensitivity is 0.1 ng/ml %%%plasminogen%%%/plasmin. This assay was used to quantitate how %%%plasminogen%%% partitions during plasma pool fractionation according to a modified Cohn process as employed at Aventis Behring. On average, only 3.1% of plasmatic %%%plasminogen%%% was detected in the cryoprecipitate, with quantitative recovery in the cryo-poor plasma. Analysis of the subsequent fractionation steps revealed that the precipitate II+III contained the largest portion of %%%plasminogen%%%. Since immunoglobulins are usually prepared from fraction II+III, we studied several IVIg products from different manufacturers. %%%Plasminogen%%% or plasmin contents ranging from <0.3 ng/mg IgG up to 2 ng/mg IgG were found. Significant differences were observed as well when other products were analyzed, like concentrates of FVIII, FIX, PCC, C1-inhibitor and fibrinogen (i.v. or as compound of a fibrin sealant). Importantly, upon testing of different lots of each product from one

manufacturer revealed excellent consistency in residual %%%plasminogen%%% levels. We conclude that the assay developed showed high sensitivity and reproducibility for the applications described. Importantly, trace amounts of %%%plasminogen%%% became detectable only due to the high sensitivity of the assay. Other %%%plasminogen%%% assays, commercially available, failed to detect this low amount of %%%plasminogen%%%. Altogether, as compared to plasma, %%%plasminogen%%% was efficiently removed by the fractionation and individual product manufacturing processes.

3/7/10
DIALOG(R)File 5:Biosis Previews(R)

0013188094 BIOSIS NO.: 200100359933
%%%Plasminogen%%% binds to disease-associated %%%prion%%% protein of multiple species
AUTHOR: Maissen Manuela; Roeckl Christiane; Glatzel Markus; Goldmann Wilfred; Aguzzi Adriano (Reprint)
AUTHOR ADDRESS: Institute of Neuropathology, University Hospital Zurich, Schmelzbergstrasse 12, CH-8091, Zurich, Switzerland**Switzerland
JOURNAL: Lancet (North American Edition) 357 (9273): p2026-2028 23 June, 2001 2001
MEDIUM: print
ISSN: 0099-5355
DOCUMENT TYPE: Letter
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The protein-only hypothesis states that the causative agent of transmissible spongiform encephalopathies is PrPSc, a conformer of the cellular protein PrPC. Therefore, reagents differentiating between PrPC and PrPSc could be diagnostically useful. %%%Plasminogen%%%, when immobilised onto magnetic beads, selectively precipitates PrPSc from mice with %%%prion%%% infected brains. We have shown that human %%%plasminogen%%% also precipitates PrPSc from brain homogenate of patients with sporadic Creutzfeldt-Jakob disease, as well as from sheep with scrapie and cows of various breeds with bovine spongiform encephalophathy (BSE). Our findings suggest that the binding of %%%plasminogen%%% to PrPSc could have diagnostic application.

3/7/11
DIALOG(R)File 5:Biosis Previews(R)

0012920328 BIOSIS NO.: 200100092167
Binding of disease-associated %%%prion%%% protein to %%%plasminogen%%%
AUTHOR: Fischer Michael B; Roeckl Christiane; Parizek Petra; Schwarz Hans Peter; Aguzzi Adriano (Reprint)
AUTHOR ADDRESS: Institute for Neuropathology, University Hospital of Zurich, CH-8091, Zurich, Switzerland**Switzerland
JOURNAL: Nature (London) 408 (6811): p479-483 23 November, 2000 2000
MEDIUM: print
ISSN: 0028-0836
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Transmissible spongiform encephalopathies are associated with accumulation of PrPSc, a conformer of a cellular protein called PrPC. PrPSc is thought to replicate by imparting its conformation onto PrPC,

yet conformational discrimination between PrPC and PrPSc has remained elusive. Because deposition of PrPSc alone is not enough to cause neuropathology, PrPSc probably damages the brain by interacting with other cellular constituents. Here we find activities in human and mouse blood which bind PrPSc and %%%prion%%% infectivity, but not PrPC. We identify %%%plasminogen%%%, a pro-protease implicated in neuronal excitotoxicity, as a PrPSc-binding protein. Binding is abolished if the conformation of PrPSc is disrupted by 6M urea or guanidine. The isolated lysine binding site 1 of %%%plasminogen%%% (kringles I-III) retains this binding activity, and binding can be competed for with lysine. Therefore, %%%plasminogen%%% represents the first endogenous factor discriminating between normal and pathological %%%prion%%% protein. This unexpected property may be exploited for diagnostic purpose.

? t s6/7/1-6

6/7/1
DIALOG(R)File 5:Biosis Previews(R)

0014402710 BIOSIS NO.: 200300361429
Stimulation of %%%plasminogen%%% activation by recombinant cellular prion protein is conserved in the NH2-terminal fragment PrP23-110.
AUTHOR: Praus Michael (Reprint); Kettelgerdes Gerhard; Baier Michael; Holzhuetter Hermann-Georg; Jungblut Peter R; Maissen Manuela; Epple Guido ; Schleuning Wolf-Dieter; Koettgen Eckart; %%%Aguzzi Adriano%%%; Gessner Reinhard
AUTHOR ADDRESS: Medizinische Fakultaet, Institut fuer Laboratoriumsmedizin und Pathobiochemie, Charite Berlin, Humboldt Universitaet zu Berlin, Augustenburger Platz I, D-13353, Berlin, Germany**Germany
AUTHOR E-MAIL ADDRESS: michael.praus@charite.de
JOURNAL: Thrombosis and Haemostasis 89 (5): p812-819 May 2003 2003
MEDIUM: print
ISSN: 0340-6245
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The cellular prion protein (PrPc), tissue-type %%%plasminogen%%% activator (t-PA) and %%%plasminogen%%% are expressed in synaptic membranes in vivo. In the central nervous system the fibrinolytic system is associated with excitotoxin-mediated neurotoxicity and Alzheimer's disease. Recently binding of the disease associated isoform of the prion protein (PrPSc) to %%%plasminogen%%% and stimulation of t-PA activity have been reported. In this study the interaction of PrPc and %%%plasminogen%%% was investigated using chromogenic assays in vitro. We found that plasmin is able to cleave recombinant PrPc at lysine residue 110 generating an NH2-terminal truncated molecule that has previously been described as a major product of PrPc metabolism. We further characterized the proteolytic fragments with respect to their ability to stimulate %%%plasminogen%%% activation in vitro. Our results show that the NH2-terminal part of PrPc spanning amino acids 23-110 (PrP23-110) together with low molecular weight heparin stimulates t-PA mediated %%%plasminogen%%% activation in vitro. The apparent rate constant was increased 57 fold in the presence of 800 nM PrP23-110. Furthermore, we compared the stimulation of t-PA activity by PrPc and beta-amyloid peptide (1-42). While the activity of the beta-amyloid was independent of low molecular weight heparin, PrP23-110 was approximately 4- and 37 fold more active than beta-amyloid in the absence or presence of low molecular weight heparin. In summary, plasmin cleaves PrPc in vitro and the liberated NH2-terminal fragment accelerates %%%plasminogen%%% activation. Cleavage of PrPc has previously been reported. Thus cleavage of PrPc

enhancing %%%plasminogen%%% activation at the cell surface could constitute a regulatory mechanism of pericellular proteolysis.

6/7/2
DIALOG(R)File 5:Biosis Previews(R)

0013962178 BIOSIS NO.: 200200555689
Prions: Health scare and biological challenge
AUTHOR: %%%Aguzzi A%%% (Reprint
AUTHOR ADDRESS: Univ. Spital Zurich, Zurich, Switzerland**Switzerland
JOURNAL: Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy 41 p516 2001 2001
MEDIUM: print
CONFERENCE/MEETING: 41st Annual Meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy Chicago, Illinois, USA September 22-25, 2001; 20010922
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Mice deficient in the normal prion protein are resistant to exposure to prion infectivity, and expression of the normal prion protein by neurons is necessary for the development of histological damage. But how do prions reach the brain after entering the body from peripheral sites? Neuroinvasion, i.e. the process by which prions march through the body of the host towards the brain, is dependent upon expression of the normal prion protein in a non-hematopoietic extracerebral site. We therefore developed the hypothesis that neuroinvasion takes place in two distinct steps: first the lymphoreticular system is diffusely colonized by the agent, while at a later time infectivity progresses from lymphoreticular organs to the central nervous system, possibly via peripheral nerves. There is an absolute requirement for B-lymphocytes in peripheral prion pathogenesis. Surprisingly, the presence of the normal prion protein is not necessary on B-lymphocytes to enable them to support this process. The mechanism of action of B lymphocytes may consist of presentation of lymphotoxin-beta to follicular dendritic cells. This paves the way to post-exposure prophylaxis strategies that exploit the anti-prion effect of soluble lymphotoxin-beta receptors. Why do follicular dendritic cells accumulate prions? We tested the hypothesis that prion uptake may be complement-mediated. Indeed, certain components of the complement system (C1q, CR1/2) proved to play an important role in pathogenesis. Progress in the understanding of pathogenesis and a elucidation of possible therapeutical and prophylactic approaches must go hand-in-hand with diagnostic procedures. With this in mind, we initiated a screen for plasma proteins that bind specifically disease-associated prion protein. %%%Plasminogen%%% was identified as such a protein. No other reagent has been shown to differentially bind the pathological prion protein while disregarding its normal counterpart. This fact may be exploitable as the basis of a sensitive diagnostic assay for BSE and for human prion diseases.

6/7/3
DIALOG(R)File 5:Biosis Previews(R)

0013188094 BIOSIS NO.: 200100359933
%%%Plasminogen%%% binds to disease-associated prion protein of multiple species
AUTHOR: Maissen Manuela; Roeckl Christiane; Glatzel Markus; Goldmann Wilfred; %%%Aguzzi Adriano%%% (Reprint

AUTHOR ADDRESS: Institute of Neuropathology, University Hospital Zurich, Schmelzbergstrasse 12, CH-8091, Zurich, Switzerland**Switzerland
JOURNAL: Lancet (North American Edition) 357 (9273): p2026-2028 23 June, 2001 2001
MEDIUM: print
ISSN: 0099-5355
DOCUMENT TYPE: Letter
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The protein-only hypothesis states that the causative agent of transmissible spongiform encephalopathies is PrPSc, a conformer of the cellular protein PrPC. Therefore, reagents differentiating between PrPC and PrPSc could be diagnostically useful. %%%Plasminogen%%%, when immobilised onto magnetic beads, selectively precipitates PrPSc from mice with prion infected brains. We have shown that human %%%plasminogen%%% also precipitates PrPSc from brain homogenate of patients with sporadic Creutzfeldt-Jakob disease, as well as from sheep with scrapie and cows of various breeds with bovine spongiform encephalophathy (BSE). Our findings suggest that the binding of %%%plasminogen%%% to PrPSc could have diagnostic application.

6/7/4
DIALOG(R)File 5:Biosis Previews(R)

0012920328 BIOSIS NO.: 200100092167
Binding of disease-associated prion protein to %%%plasminogen%%%
AUTHOR: Fischer Michael B; Roeckl Christiane; Parizek Petra; Schwarz Hans Peter; %%%Aguzzi Adriano%%% (Reprint
AUTHOR ADDRESS: Institute for Neuropathology, University Hospital of Zurich, CH-8091, Zurich, Switzerland**Switzerland
JOURNAL: Nature (London) 408 (6811): p479-483 23 November, 2000 2000
MEDIUM: print
ISSN: 0028-0836
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Transmissible spongiform encephalopathies are associated with accumulation of PrPSc, a conformer of a cellular protein called PrPC. PrPSc is thought to replicate by imparting its conformation onto PrPC, yet conformational discrimination between PrPC and PrPSc has remained elusive. Because deposition of PrPSc alone is not enough to cause neuropathology, PrPSc probably damages the brain by interacting with other cellular constituents. Here we find activities in human and mouse blood which bind PrPSc and prion infectivity, but not PrPC. We identify %%%plasminogen%%%, a pro-protease implicated in neuronal excitotoxicity, as a PrPSc-binding protein. Binding is abolished if the conformation of PrPSc is disrupted by 6M urea or guanidine. The isolated lysine binding site 1 of %%%plasminogen%%% (kringles I-III) retains this binding activity, and binding can be competed for with lysine. Therefore, %%%plasminogen%%% represents the first endogenous factor discriminating between normal and pathological prion protein. This unexpected property may be exploited for diagnostic purpose.

6/7/5
DIALOG(R)File 5:Biosis Previews(R)

0010094659 BIOSIS NO.: 199698562492

Analysis of the human tissue-type %%%plasminogen%%% activator gene promoter activity during embryogenesis of transgenic mice and rats
AUTHOR: Theuring F (Reprint); %%%Aguzzi A%%%; Kropp C (Reprint); Wohn K-D (Reprint); Hoffmann S; Schleuning W D (Reprint
AUTHOR ADDRESS: Schering Res. Lab., D-13342 Berlin, Germany**Germany
JOURNAL: Fibrinolysis 9 (5): p277-287 1995 1995
ISSN: 0268-9499
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The spatio-temporal pattern of lacZ reporter gene expression, directed by two fragments of the human tissue-type %%%plasminogen%%% activator gene promoter comprising 3.0 kb or 1.4 kb of upstream sequence, was analyzed during midgestational development of transgenic mice and rats. In both species, the 3.0 kb fragment directed expression during development to discrete regions of the nervous system and some specific nonneuronal sites, but not to the vascular system. Reporter gene activity directed during development by the 1.4 kb fragment was more variable, including components of nervous and vascular system and additional organs. The deletion of control elements apparently renders the transgene vulnerable to positional effects. The gain of vascular expression could be due to the deletion of a repressor/silencer element. In both species, reporter gene activity mediated by the human t-PA gene promoter is concentrated in areas of active cell migration, particularly of neural crest derivatives, corroborating previous findings suggesting a role for t-PA in tissue remodeling during neuronal development.

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0009624131 BIOSIS NO.: 199598091964
Improved in situ beta-galactosidase staining for histological analysis of transgenic mice
AUTHOR: %%%Aguzzi Adriano%%% (Reprint); Theuring Franz
AUTHOR ADDRESS: Inst. Neuropathol., Schmelzbergstrasse 12, CH-8091 Zurich, Switzerland**Switzerland
JOURNAL: Histochemistry 102 (6): p477-481 1994 1994
ISSN: 0301-5564
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The present study describes a novel method for the histochemical demonstration of beta-galactosidase activity on tissue sections. We have replaced 5-bromo-4-chloro-3-indolyl-beta-D-galactoside (X-Gal) with 5-bromoindolyl-beta-o-galactopyranoside (Bluo-Gal) as a chromogenic substrate for the bacterial beta-galactosidase (lacZ). After beta-galactosidic cleavage, Bluo-Gal precipitates in form of fine birefringent crystals, whereas X-gal gives rise to an amorphous precipitate. Upon microscopic examination under polarized light, the crystals emit a strong signal consisting of yellow reflected light. This property of Bluo-Gal results in greatly enhanced sensitivity of the staining method for beta-galactosidase and allows for optimal morphological resolution. To exemplify the applications of this technique, the expression is demonstrated in transgenic mice of beta-galactosidase driven by a fragment of the human tissue-type %%%plasminogen%%% activator promoter.

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